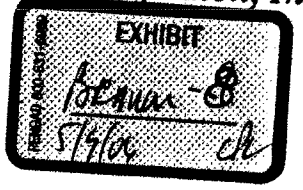
PSJ17 Exh 47

DRAFT

QUALITY ASSURANCE MEMORANDUM

Cephalon, Inc.



To: QA File

From: Dave Brennan

Subject: Internal Audit of Actiq Risk Management Program, 2nd Qtr 2003

Copies: Tim Sheehan Carol Marchione Bob Bader Dan Winkelman

Executive Summary:

Department: Regulatory Affairs – Actiq Risk Management Program

Location: West Chester, PA

Dates of Audit: 1 April and 16 May 2003

Audit Team: Dave Brennan

Participants: Tracie Parker – Regulatory Affairs
Kay McGhee – Global Product Safety
Dan Winkelman – Marketing

Objective: Audit Actiq Risk Management Program reporting activities to determine compliance with filing commitments.

Conclusion: Based on the findings of this audit, Cephalon is not in compliance with the commitments communicated in the Risk Management Program dated August 1, 2001 filed with Actiq NDA #20-747. The identified issues will be communicated to Regulatory Affairs Management for response and corrective action.

#13 3/15 when —

Add "Confidential" – Do not copy.

Audit Results:

Reference Audit Plan and RMP Table of Contents for applicable section numbers.

8.0 Surveillance Goals and Activities

8.1 Direct Patient Feedback

8.1.1 Chain Pharmacy Call Back System

8.1.1.1 Verify documentation that patients receive a follow-up phone call by a company pharmacist.

Walgreen's and CVS participate in this program and make the actual patient contacts. The information is then transferred to Cephalon. Hard copy documents from Walgreen's are held by Product Safety. CVS data is transmitted electronically and stored on J:\. Walgreen's data is manually entered by Product Safety into an Access database also stored on J:\.

8.1.1.2 Verify questionnaire.

The questionnaire matches the RMP.

8.1.1.3 Verify 1000 patients per chain per year.

The 4th quarter 2002 report (cumulative) had 5,094 responses. This is more than the minimum required total of 4000 (1000 times top 4 chains) per year but responses are not reported by chain.

8.1.1.4 Verify top 4 chains included.

8.1.1.4.a. RiteAid 8.1.1.4.b. Eckerd 8.1.1.4.c. Walgreen's 8.1.1.4.d. Merk Medco

Participating chains are not identified in the report. Walgreen's may be the only chain represented. The **RMP Process Guide** indicates CVS Procare data is included too but this does not seem to match current practice. This paragraph of the RMP indicates that this program will only be conducted for the first year of sales. It also indicates that after 1 year the company will negotiate with FDA to discontinue the patient survey.

8.2 Prescription Monitoring

8.2.1 IMS Xponent

NDC Source Prescriber is used instead of IMS Exponent. NDC Source Prescriber data is not reported. We only report that no specialty exceeds 15%.

8.2.1.1 Verify that data is collected and analyzed monthly.

SOP 0426-J02, section 4.3 instructs this to be done quarterly. Although quarterly is sufficient for FDA report, it does not comply with commitment in the RMP that analysis includes data between 28 and 58 days old.

8.2.1.2 Verify that data analysis includes ratio.

SOP 0426-J02 indicates that only the number of prescriptions and proportion of prescriptions by specialty are included in the report. There is no ratio of "appropriate patient selection" vs. "inappropriate patient selection" as required by the RMP.

8.2.1.3 Verify ratio of appropriate patient selection exceeds 85% (in compliance with 9.1.2)

The ratio is not determined or reported as required by the RMP.

8.2.1.4 Verify "appropriate" and "inappropriate" are defined.

SOP 0426-J02, section 4.5 lists Oncology, Hematology and Pain Specialists (including Anesthesiologists) as physician specialty categories exempt from the 15% requirement.

8.2.2 IMS National Disease and Therapeutic Index

This database is purchased from IMS as an excel spreadsheet and is saved on I:\

8.2.2.1 Verify that NDTI data is analyzed by specialty.

NDTI data could be analyzed by specialty but the results are too small to be meaningfully broken down further.

8.2.2.2 Verify that NDTI data is analyzed by indication.

Only diagnosis code is included in the analysis. According to Market Research, this is not "indication" but "disease". Market Research does not analyze by indication.

8.2.2.3 Verify analysis is reported quarterly.

The data is included in each report as appendix 2. It is only reported by the one variable, diagnosis code or "disease", and not by "indication" or specialty.

8.2.3 Wholesaler Data

8.2.3.1 Verify that retail pharmacy sales information is collected from wholesalers.

Sales Operations collects this data and distributes it quarterly to the Sales Managers. It is sorted by territory number. Sales Managers are instructed to identify new pharmacies in their territory to ensure that the pharmacists at these sites are familiar with the "point of dispensing" resources available to them. They are also reminded to prompt the pharmacist to ask the patient about the presence of children and verify opioid tolerance.

8.2.3.2 Verify information is communicated to Oncology Sales Specialists (OSS).

The reports indicate that the data is being sent to OSS. 4th Qtr 2002 was distributed via e-mail to all Sales PCS Managers and all Sales PCS Reps.

8.2.3.3 Verify OSS is following up with each regarding "Point of Dispensing" interventions (Section 7.0).

This could not be verified during the audit. The reps are instructed quarterly to prompt the new pharmacists regarding correct interventions.

8.2.3.4 Verify wholesaler representative calls high volume wholesalers every two months.

No documentation could be found to demonstrate that this occurs. The quarterly report does not mention it.

8.2.3.5 Verify new pharmacies are communicated to OSS.

Sales Operations collects pharmacy data and distributes it quarterly to the Sales Managers and Sales Reps. Managers are instructed to identify new pharmacies in their territory from the list provided.

8.2.3.6 Verify compliance to "Point of Dispensing" is evaluated.

"Point of Dispensing" is evaluated via direct patient feedback (section 8.1) so only Walgreen's "point of dispensing" system is evaluated. No other "point of dispensing" evaluation is performed.

8.2.3.7 Verify violations (and interventions) are reported.

Data is not individually collected. The cumulative percent responses are tabulated and reported. The survey would indicate that "point of dispensing" systems are not being

followed. For example, the 15th quarterly report indicates that over 75% of the patients interviewed did not receive a Welcome Kit. The report does not indicate any interventions to correct the violation.

8.3 Adverse Events

8.3.1 Cephalon SOP

8.3.1.1 Verify Actiq complaints are logged and investigated.

Professional Services receives and logs complaints according to **SOP 0330-Q04**, Product Complaints – U.S. Commercial Operations.

8.3.2 Special Safety Commitments

8.3.2.1 Verify Special Safety adverse experiences are reported.

Adverse experiences are summarized in the quarterly report.

8.3.3 Literature Monitoring

The **RMP Process Guide** instructs Product Safety to describe mentions in literature when reporting to Regulatory Affairs. **SOP 0326-D01**, Post Marketing Adverse Drug Experience Monitoring and Reporting – Cephalon U.S., section 5.1.2 describes the process by which the literature searches are conducted.

8.3.3.1 Verify literature review system is in place.

Product Safety contracts this service via ClinTrace. Articles are scanned by product name.

8.3.3.2 Verify literature review is conducted monthly.

Monthly a summary report of literature hits is provided to Product Safety.

8.3.3.3 Verify findings included in quarterly report.

Findings of adverse events reported in the literature should be included in the quarterly report. This could not be verified since no examples were observed. **(Have we ever had a hit here?)**

8.4 Poisoning and Overdose

8.4.1 Central 1-800 Poison Control Number

8.4.1.1 Verify Poison Control findings are included in quarterly report.

Product Safety contracts this to Rocky Mountain Poison and Drug Center (RMPDC). Calls are cataloged in the report.

8.4.2 Toxic Exposure Surveillance System

8.4.2.1 Verify latest TESS data was evaluated and reported.

TESS data is available at the American Association of Poison Control Centers web site (www.aapcc.org). This site is consulted quarterly. An annual hardcopy TESS report is also provided by AAPCC. The web data is shown in the quarterly report.

8.5 Abuse

8.5.1 Routine Cephalon Interaction with DEA

8.5.1.1 Verify routine communication with DEA.

No documentation of routine DEA or state agency interaction regarding Actiq Risk Management could be located.

(8.5.2 old) Abbott Exception System (2/99 only – deleted 8/01)

Not evaluated. Obsolete.

8.5.2 Drug Abuse Warning Network

8.5.2.1 Verify DAWN is monitored.

DAWN data is available via the web and is shown in the report, however, there is no Actiq information in this report and the report cannot be related to Actiq abuse. The reported activity is related to Fentanyl only.

8.5.3 State Drug Control Authorities or State Boards of Pharmacy

8.5.3.1 Verify state information is reported.

No state information is reported. We do not actively solicit information. We do not have a mechanism to track if we receive unsolicited information. Paragraph 8.5.1 implies that we will actively interact with both DEA and state agencies.

8.6 Promotional Message Audit

8.6.1 Verify the promotional message testing is conducted every 6 months.

Marketing contracts the promotional message audits to Strategic Business Research. 50 physicians are telephoned each 6 months and interviewed. SBR provides a summary of the questionnaire results. This summary is reported in appendix 4. The contractor does not provide individual responses.

8.6.2 Verify retraining or discipline.

N/A

9.0 Intervention

9.1 Off-Label Usage

9.1.1 Individual Prescribers

9.1.1.1 Verify that individual prescribing patterns are monitored.

Individual prescribers are not monitored. When an individual is noted to prescribe off label based on ADE reporting and the prescribing doctor is identified in the ADE, a form letter is mailed to the doctor. Appendix 3 of the quarterly report lists individual events and identifies when a letter was sent to the prescribing doctor.

9.1.2 Groups of Prescribers

This section is omitted from the quarterly report. **SOP 0426-J02**, section 4.5 indicates that Marketing will report any single physician specialty category (excepting listed exemptions) exceeding 15% to Regulatory Affairs and Product Safety. The RMP says that potential off label use exceeding 15% will be reported to the FDA. The SOP does not comply with the RMP commitment. This section is related to the ratio reporting requirement in section 8.2.1.

9.1.2.1 Verify that potential off-label use is evaluated.

Physician specialty prescribing is monitored via data from NDC Source Prescriber. The list of exempt physician specialties in **SOP 0426-J02** does not seem to be used as the guide for determining which specialties represent potential off-label vs. not off-label. Since no individual group exceeds 15%, no analysis of the data is performed. Approximately 85 specialty groups are represented. The raw data is reported to Regulatory Affairs but not included in the quarterly reports.

9.1.2.2 Verify that potential off-label use does not exceed 15%.

Since no individual specialty exceeds 15% and only 3 specialties are listed as exempt or "appropriate", one could assume that the "appropriate" specialties represent no

more than 45% of total prescriptions, leaving the other 55% minimum in unlisted or "inappropriate" specialties.

9.2 Accidental Ingestion

9.2.1 Verify that unintentional pediatric exposure initiates adverse event procedures. Accidental ingestion is reported as an adverse event.

10.0 FDA Reporting

10.1 Verify that 15-day alerts are going to:

10.1.a. FDA

Per Global Product Safety SOPs, i.e. Central Document Room

10.1.b. Division of Prescription Drug Compliance and Surveillance

RMP says to send here in addition to CFR Reporting requirements. Regulatory Affairs indicates that this is the CFR reporting requirement. The CFR indicates that the reports are to be sent to the Central Document Room.

10.1.c. Division of Anesthetic, Critical Care, and Addiction Drug Products

RMP says we will send these here too, but Regulatory Affairs says that phone call from this division says it is not necessary.

10.2 Verify that FDA reports are quarterly.

12^{th} through 15^{th} quarterly reports were reviewed for this audit. These represent the 4 quarterly reports for 2002. 12^{th} quarter (1^{st} quarter 2002) was submitted 5/31/02. 14^{th} quarter (3^{rd} quarter 2002) was submitted 12/9/2002. 13 and 15 did not include cover letters so their submission dates were not verified.

Records and Documents Reviewed:

1. Actiq Risk Management Program dated 2/9/99
2. Actiq Risk Management Program dated 8/1/01
3. Actiq Risk Management Program 12^{th}, 13^{th}, 14^{th} and 15^{th} quarterly reports representing 1^{st}, 2^{nd}, 3^{rd} and 4^{th} quarters of 2002
4. Memos to File from T. Parker explaining the various RMP sections, dated between 3/6/03 and 3/25/03. These are attached to the report.
5. Actiq Global Product Safety RMP Process Guideline dated 1/7/03
6. SOP 0326-D01 – Post Marketing Adverse Drug Experience Monitoring and Reporting – Cephalon U.S., 12/7/01
7. SOP 0256-D08 – Adverse Drug Experience, Product Complaint, and Medical Information Referrals to U.S. Product Safety and Professional Services – Cephalon U.S., 7/19/01
8. SOP 0321-D08 – Response to Requests for Medical Information, 11/13/01
9. SOP 0330-Q04 – Product Complaints – U.S. Commercial Operations, 10/29/02

Items requiring follow-up:

1. The 4 listed pharmacy chains are not included as required by section 8.1.1. Section 8.0 further commits that if any of the 4 organizations are unable to participate, Cephalon will substitute another supplier. Only Walgreen's is represented.

2. The Actiq Global Product Safety RMP Process Guideline of 1/7/03 indicates that CVS Procare participates in the pharmacy call back system. CVS Procare data is no longer received.

3. NDC Source Prescriber is used in place of IMS Exponent specified in section 8.2.1.

4. The proportion of prescriptions being written by specialties representing "appropriate" patient selection to those being written by specialties representing "inappropriate" patient selection is not calculated or reported as required by section 8.2.1.

5. Prescriptions by specialties representing "inappropriate" patient selection exceed the 15% reporting threshold of potential off label usage specified in section 9.1.2. This is not reported.

6. NDC Source Prescriber data is analyzed once per quarter per SOP 0426-J02. Section 8.2.1 requires the data to be analyzed monthly to maintain a 28-58 day age limit on the analysis.

7. NDTI data is not analyzed by specialty as required by section 8.2.2.

8. NDTI data is analyzed using diagnosis code. Market Research indicates that diagnosis code analysis is by "disease", not by "indication" as required by section 8.2.2.

9. There is no documentation that bi-monthly calls are made to high volume wholesalers to identify new pharmacies as required by section 8.2.3. This is not included in the report.

10. Cephalon does not conduct monitoring of "Point of Dispensing" compliance as required by section 8.2.3 beyond direct patient feedback from Walgreen's. Violations identified from the Walgreen's surveys are not noted and no interventions are documented as required by section 8.2.3.

11. There is no documentation that Cephalon has routine interaction with DEA or state authorities regarding Actiq Risk Management as required by sections 8.5.1 and 8.5.3.

12. **DAWN data does not indicate Actiq abuse as implied by section 8.5.2. The database reports only based on active ingredient.**

13. **There is no mechanism to track the receipt of unsolicited information from state authorities to ensure that it is reported as required by section 8.5.3.**

14. **The quarterly RMP report omits section 9.1.2. This section requires that inappropriate prescriptions representing potential off label usage greater than 15% of the total Actiq prescriptions will prompt Cephalon to offer educational programs to the various professional societies. It further specifies that if the potential off label usage greater than 15% continues for two additional quarters, Cephalon will initiate an "aggressive" education campaign. No documentation of intervention could be found.**

15. **SOP 0426-J02 indicates that only individual specialties with prescription rates exceeding 15% of the total Actiq prescriptions will be reported to Regulatory Affairs. There are approximately 85 specialties reported, 3 of which are included in the list of exemptions in the SOP. This does not comply with the requirement in section 9.1.2 that prescriptions representing potential off label usage greater than 15% prompts action.**

16. **Reporting requirements for 15-day Alerts in section 10.0 are unclear. The Division of Anesthetic, Critical Care, and Addiction Drug Products does not receive 15-day Alerts as required by section 10.0. The section also clearly indicates that in addition to the CFR reporting requirements, the Division of Prescription Drug Compliance and Surveillance will receive notification of 15-day Alerts.**

Conclusion:

Based on the findings of this audit, Cephalon is not in compliance with the commitments communicated in the Risk Management Program dated August 1, 2001 filed with Actiq NDA #20-747. The identified issues will be communicated to Regulatory Affairs Management for response and corrective action.